1. **Priority**

Again it is asserted that neither provisional application appears to provide adequate written support. Applicants respectfully disagree and as stated in previous responses assert that there has been sufficient disclosure in the provisional applications, particularly in Example 2 of both applications.

2. **The Rejections Under 35 U.S.C. §112, Second Paragraph**

Claims 53-60 are considered to be indefinite in that they only describe the protein bound by the antibody by the arbitrary protein name "heparin binding proteins (HBP)." It is suggested that any limitations regarding the HBP be written to *clearly modify the HBP bound by the antibody* administered in the method, e.g. by indicating that the HBP bound by the antibody is the same as that produced by the mammal ("wherein said antibody binds to an epitope of *said* HBP").

In response, Applicants have amended claim 53 to recite that characteristics recited in claim 53 are indeed characteristics of HBP. Furthermore, in response to the Examiner's suggestion, it is receipted "wherein said antibody binds to an epitope of said HBP".

In view of the amendment of claim 53, the rejection under 35 U.S.C. 112, second paragraph have been overcome. Therefore, Applicants respectfully request that the rejection be withdrawn.

3. **The Rejection Under 35 U.S.C. §112, First Paragraph**

Claims 53-60 have been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The specification as originally filed does not provide support for the invention as now claimed.

Specifically, it is asserted that the specification does not appear to provide an adequate written description of "antibody that binds an epitope of HBP which interacts *with kininogen*". The specification is objected to for the same reason. In the Examiner's view, no evidence is provided that an epitope of HBP binds to kininogen.

Applicants respectfully traverse the rejection and objection. First Applicants note that the Examiner has conceded that Applicant provides evidence that blocking HBP (by binding to aprotinin) or blocking various steps in the direct activation of bradykinin inhibits the HBP-induced increase in EC permeability and that the Renne Declaration provides data to support that HBP can *displace* HK assembled on the surface of endothelial cells or on immobilized heparin sulfate. It is Applicants view that these results do indeed provide evidence of interaction of HBP with kininogen. According to the Webster's Collegiate Dictionary, "interact" is defined as "to act upon one another". In Applicants, view, an epitope of HBP is certainly interacting with kininogen when it increases EC permeability and when it displaces HK assembled on the surface of endothelial cells. It is certainly not necessary that HBP physically bind to kininogen for an interaction to take place.

In view of the above arguments, Applicants assert that the rejection has been overcome. Therefore, Applicants respectfully request that the rejection be withdrawn.

4. The Rejection Under 35 U.S.C. §102(e)

Claims 53-55 and 60 have been rejected over Oppenhelm et al.. In the Examiner's view, the claimed functional limitation of decreasing release of bradykinin and altering endothelial cell permeability would be an inherent property of a method comprising administering an anti CAP37/HBP antibody to reduce or inhibit an inflammatory disorder and that any antibody that binds HBP and inhibits inflammation must bind the same epitope of HBP.

Applicants respectfully traverse the rejection. HBP contains a number of epitopes. In Applicants view, just because an antibody binds to an epitope on HBP does not necessarily mean that such an antibody would bind an epitope of heparin-binding protein which interacts with kininogen, and that said binding of said antibody to said HBP would actually decrease release of bradykinin and in an amount effective to attenuate said alterations in endothelial cell permeability in said mammal.

Therefore, Oppenholm does not anticipate the claims and Applicants respectfully request that the rejection be withdrawn.

5. **The Rejection Under 35 U.S.C. §103**

Claims 56-59 have been rejected under 35 U.S.C. §103 as being unpatentable over Oppenhelm et al. as evidenced by Rasmussen et al. in view of Grunfield et al. Applicants traverse the rejection. As noted above, Oppenhelm only discloses an antibody that binds HBP and inhibits inflammation. There is absolutely no suggestion that HBP contains an epitope that interacts with kininogen. There would be no motivation to combine Grunfield with Oppenhelm since the subject matter is different. Specifically, Grunfield is directed to the use of PTHrP antagonists. The Examples in Grunfield et al. are directed to showing the effect of antiserum directed against PTHrP on LPS-induced lethality; no other therapeutic agent was used. It is pointed out in Grunfield that though PTHrP antagonists can be used with other therapeutic agents, the combination therapy is optional (see paragraph bridging columns 4 and 5). Therefore, claims 56-69 would not be obvious over the cited references.

6. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone at (914) 712-0093 if there are any questions concerning this amendment or application.

Respectfully submitted,

Date:

Cheryl H. Agris, Reg. No. 34,086
Outside Counsel for
Novo Nordisk Pharmaceuticals, Inc.
100 College Road West
Princeton, New Jersey 08740

AMENDED SPECIFICATION (MARKED UP VERSION)

Please amend the paragraph on page 10, lines 10-13 to read as follows:

~~Figure 5~~ Figures 5A and 5B shows inhibition of bradykinin- and HBP-induced increase in EC permeability with monoclonal antibody MBK3 to bradykinin. Bradykinin (100 nM; Figure 5a) or HBP (75 μg/ml; Figure 5b) is administered at time zero to the lamina side of EC monolayers pre-incubated with mAb MBK3 (40 μg/ml).

Please amend the paragraph on page 11, lines 2-6 to read as follows:

~~Figure 11~~Figures 11 A-C show: Saturation of native HBP, [R23S,F25E]HBP, and [G175Q]HBP with (A) ^{3}H-LPS and (B) Competition for ^{125}I-BPTI binding with fixed, increasing concentrations of unlabeled BPTI. (C) Concentrations of ^{125}I-BPTI shown in % 0 nM of unlabeled BPTI. The apparent difference in binding between HBP and [R23S,F25E]HBP is discussed in the "Results" section. Bars indicate standard deviations.

AMENDED CLAIMS (MARKED UP VERSION)

53. (amended) A method for preventing or treating a disorder resulting from release of bradykinin and alterations in endothelial cell permeability in a mammal, wherein said mammal produces heparin binding protein (HBP) ~~that~~ wherein said heparin-binding protein is (i) is proteolytically inactive; (ii) is stored in the azurophil granules of polymorphonuclear leukocytes; (iii) is a chemoattractant for monocytes and/or activates monocytes; (iv) has at least about an 80% identity with the amino acid sequence set forth in SEQ ID NO:1; (v) interacts with kininogen resulting in release of bradykinin and (vi) induces alterations in endothelial cell permeability in said mammal, said method comprising administering to said mammal in need thereof, an amount of an anti-heparin binding protein antibody, wherein said antibody binds to an epitope of said heparin-binding protein ~~which interacts with kininogen~~, in an amount effective to decrease release of bradykinin and in an amount effective to attenuate said alterations in endothelial cell permeability in said mammal.